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PATENT COOPERATION TREATY

RECD 14 SEP 2001

WIPO PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

RECD PCT/PTO 13 DEC 2001

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
SCB/51868001		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05592	14/06/2000	14/06/1999

International Patent Classification (IPC) or national classification and IPC
C12N15/12

Applicant
JANSSEN PHARMACEUTICA N.V. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 (+4 pages amended seq. list.) sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/12/2000	12.09.2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05592

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-45	as originally filed			

Claims, No.:

1-33	as received on	22/08/2001	with letter of	20/08/2001

Drawings, sheets:

1/8,2/8,4/8-8/8	as originally filed			
3/8	as received on	22/08/2001	with letter of	20/08/2001

Sequence listing part of the description, pages:

1-4, filed with the letter of 20.08.01

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☒ furnished subsequently to this Authority in written form.
   - ☒ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:
   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
   see separate sheet

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

   ☐ copy of the earlier application whose priority has been claimed.

   ☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

   Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
   see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 20, 21, 25, 26, 27(part).

because:

   ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

   ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 20, 21, 25, 26,

27(part) are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 20, 21, 25, 26, 27(part).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-4, 6-14, 18, 19, 22-24, 28, 30, 31, 33
	No:	Claims	5, 15, 16, 17, 27, 29 and 32
Inventive step (IS)	Yes:	Claims	1-4, 6-14, 18, 19, 22-24, 28, 30, 31, 33
	No:	Claims	5, 15, 16, 17, 27, 29 and 32
Industrial applicability (IA)	Yes:	Claims	1-19, 22-24, 27-33
	No:	Claims	

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

I. Basis

The amendments to the sequence of human 5-HT4(h) in Fig. p. 3/8 and in the sequence listing cannot be accepted since it is not an obvious correction of an error. The DNA and Protein sequences are obviously inconsistent, yet it is not obvious which of the two sequences was defective. The argument that the protein sequence must be based on the translation of the DNA sequence in the Figures does not hold. Figures and sequences can be assembled in a number of ways - further one would not expect a computer to make such a mistake in the actual translation process. A skilled person could equally assume that the protein was correct but that the DNA sequence was incorrect (i.e. that there was no stop codon at the disputed position in the human gene). This view could be considered more likely since one would expect an applicant to be more surprised by a longer protein than by a nucleic acid change which he may not even notice in the present context. Hence, the correction performed by the applicant is an unallowable amendment. A correction of the DNA sequence would similarly not be permitted. *It is noted that applicant could still obtain cover for the correct human splice variant by claiming a protein encoded by the DNA sequence as filed.*

The claims have been examined as though the sequence and figures had not been amended.

II. Priority

The present claims appear to be all entitled to priority from 14.06.99.

III. No Opinion

Claims 20, 21, 25, 26, 27(part) were not searched and consequently cannot be examined. The claims relate to modulators which are technically not defined.

V. Reasoned statement on Novelty, Inventive Step and Industrial Applicability

The documents mentioned in the present International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first

document of the search report etc.

- **Novelty (Art.33(2) PCT)**

Viewing the relevant prior art in chronological order:

D3 discloses the human 5-HT4 receptor. Comparing this receptor to the splice variant identified by the applicant (see present Seq.ID No.8) one sees that the V at the beginning is missing, 14 internal aa are missing, and the C-terminal sequence APGTMT... is missing.
D3, being a patent application, discloses nucleic acids / vectors / host cells + vectors / probes /antisense oligos / proteins / methods production / antibodies / pharmaceutical compositions / assays for interacting molecules using cells or membranes / methods of treatment. Because many of the present claims are not limited to the novel splice variant and cover e.g. antisense molecules which could bind the sequence of 5-HT4 as disclosed in D3 (i.e. parts that are shared between the receptor of D3 and applicants splice variant), D3 anticipates present claims 5, 15, 16, 17, 27, 29 and 32.

D2 reports the cloning of 3 further splice variants of h5-HT4: variants (b), (c) and (d). Showed identical pharmacological profile to known 5-HT4, but found differences in way they trigger signal transduction. The (c) and (d) variants had not been described in any species previously. Tissue distribution was examined by PCR. The cDNAs were expressed in COS-7 cells, whereon the receptor functions were then studied. Tested agonists and antagonists effect on 5-HT mediated receptor activation. D2 does not suggest looking for further splice variants, neither does it rule their existence out. D2 anticipates claims 5 and 15 for analagous reason as objections based on D3.

- **Inventive Step (Art.33(3) PCT)**

Once the clarity objections have been dealt with adequately, and the present claims have been strictly limited to the novel splice variant 5-$HT_{4(h)}$, inventive step will be acknowledged for the claimed subject-matter.

- **Industrial Applicability (Art.33(4) PCT)**

The present claims appear to have industrial applicability.

VIII. **Certain observations**

- **Clarity (Art.6 PCT)**

Claims 1, 11, 13, 18 - Need to delete "encoding a functional equivalent, derivative or bioprecursor".
Other known splice variants share functions with the present variant.
Argumentation that specific functional differences have been shown is fine as a basis for using such specific differences as technical features in the claims.
Anyhow, a functional equivalent cannot be allowed without some associated sequence limitation. Otherwise, a completely different peptide which applicant has not enabled a skilled person to identify, which happens to have some function in common, would fall within the scope of the claim. This is clearly unacceptable.
Further, p.12 merely specifies "functional equivalents" as exhibiting the same properties and functionality. The properties or functionalities are however not defined. No two proteins will have exactly the same properties (the sequence is a property too as is the antigenicity). If the statement is taken to mean "some identical properties" then proteins with the same melting point or having property of a certain shared linear epitope (e.g. splice variants) will fall within claim.
Hence, the description does not provide a clear basis for defining the term either.
Indeed often, functional equivalents are suggested to include proteins sharing antigenic properties i.e. an epiptope with the actual protein provided. Such broad definitions are however generally not acceptable and in case of splice variants even less so since majority of epitopes in case of a splice variant are shared.
Regarding the term "derivative" - this is meaningless unless a process of derivation is clearly defined which delimits the structural variation of the product obtained by the process of derivation.
Regarding "Bioprecursor" - this can be a single amino acid, which is clearly a bioprecursor of a polypeptide.

Claims 5, 15 - define "high stringency" in claims

Claim 29 - antibodies should be defined by an exact sequence to which they bind

Claims

1. The nucleic acid molecule of claim 1 encoding a human 5-$HT_{4(h)}$ receptor comprising the amino acid sequence illustrated in SEQ ID NO: 2 or encoding a functional equivalent, derivative or bioprecursor of said receptor.

2. A nucleic acid molecule according to claim 1 which is a DNA molecule.

3. A nucleic acid molecule according to claim 2, wherein said DNA molecule is a cDNA molecule.

4. A nucleic acid molecule according to any of claims 2 to 4 comprising the sequence of SEQ ID NO: 1.

5. A nucleic acid molecule capable of hybridising to the molecule of any of claims 1 to 4 or the complementary sequences thereto under conditions of high stringency.

6. A human 5-$HT_{4(h)}$ receptor encoded by the nucleic acid molecule according to any of claims 1 to 4.

7. A DNA expression vector comprising a nucleic acid molecule according to any of claims 2 to 4.

8. A host cell transformed or transfected with the vector of claim 7.

9. A host cell according to claim 8, which cell is a mammalian cell.

10. A host cell according to claim 9, which mammalian cell is a COS-7 cell.

11. A transgenic cell, tissue or organism comprising a transgene capable of expressing a human 5-$HT_{4(h)}$ receptor protein comprising the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence of a functional equivalent, derivative or bioprecursor of said receptor.

12. A transgenic cell, tissue or organism according to claim 11 wherein said transgene comprises a nucleic acid molecule according to any of claims 1 to 4.

13. A human 5-$HT_{4(h)}$ receptor protein or a functional equivalent, derivative or bioprecursor thereof, expressed by the cell according to any of claims 8 to 10 or the cell tissue or organism according to claim 11.

14. A HEK 293 or COS-7 5-$HT_{4(h)}$ cell line transfected with the expression vector of claim 7.

15. An antisense molecule comprising a nucleic acid molecule which is capable of hybridising to the nucleic acid of any of claims 1 to 4 under conditions of high stringency.

16. A pharmaceutical composition comprising a molecule according to claim 15 together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

17. An antisense molecule according to claim 15 for use as a medicament.

18. A purified or isolated human 5-$HT_{4(h)}$ receptor protein comprising the amino acid sequence of SEQ ID NO: 2 or the amino acid sequence of a

functional equivalent, derivative, fragment or bioprecursor of said sequence.

19. A pharmaceutical composition comprising a molecule according to any of claims 1 to 4 together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

20. An antagonist or an agonist of a ligand of the human 5-$HT_{4(h)}$ receptor protein according to any of claims 13 or 18.

21. A pharmaceutical composition comprising an antagonist or an agonist according to claim 20 together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

22. A method of determining whether a compound is an agonist or an antagonist of a ligand of a human 5-$HT_{4(h)}$ receptor, which method comprises contacting a cell according to any of claims 6 to 9 expressing said receptor protein with said compound in the presence of said ligand and monitoring cAMP formation in said cell.

23. A method according to claim 22 wherein said cell is a human cell.

24. A method of determining whether a compound binds to a human 5-$HT_{4(h)}$ receptor which method comprises contacting a cell, according to any of claims 8 to 11 or a membrane preparation comprising said receptor, with said compound and establishing the binding affinity of said compound for said receptor.

25. A compound identifiable as an agonist or

antagonist according to the method of claim 23 or 24.

26. A compound according to claim 25 for use as a medicament.

27. Use of a compound identifiable according to the method of claim 25 or an antisense molecule according to claim 15 in the manufacture of a medicament for the treatment of any of heartburn, reflux, esophagitis, Barrett's esophagus, esophageal cancer, achalasia, esophageal stenosis, esophagel spasms, esophageal hiatal hernia or other esophageal motility disorders, oesophageal irritation, such as asthma, bronchospasms, aspiration and its consequences (bronchitis, (broncho)pneumonia, bronchiectasia) and other diseases of the lower oesophageal sphincter, or achalasia; oesophageal stenosis (due to systemic sclerosis, tumours, burns, or the like) or compression, oesophageal spasms or other oesophageal motility disorders, asthma, irritable bowel syndrome, bronchospasms and other airway disorders possibly connected with oesophageal irritation aspiration and its consequence (bronchitis, (broncho)pneumonia; bronchiectasia); (hiatus) hernia; denervation of the oesophagus (e.g. after certain types of trauma or surgery), disturbances in oesophageal innervation.

28. A pharmaceutical composition comprising a compound according to claim 26 together with a pharmaceutically acceptable carrier diluent or excipient therefor.

29. An antibody specific for a human 5-$HT_{4(b)}$ receptor

according to claim 6 or 18.

30. A kit for determining whether a compound is an agonist or an antagonist of a 5-$HT_{4(h)}$ ligand, which kit comprises a cell according to any of claims 8 to 11, means for contacting said compound and said ligand with said cell and means for measuring cAMP formation is said cell.

31. A kit according to claim 30 wherein said cell is a COS-7 cell.

32. A pharmaceutical composition incorporating the nucleic acid sequence according to any of claims 1 to 4, or the antibody according to claim 29, together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

33. A method of identifying a ligand for 5-$HT_{4(h)}$ receptor, which method comprises contacting a cell expressing said receptor with said compound to be tested and monitoring the level of any 5-$HT_{4(h)}$ mediated functional or biological response.

: 310975: CDH: JLG: LONDOCS

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h5HT4B : MDKLDANVSSEEGFGSVEKVVLLTFLSTVILMAILGNLLVMVAVCWDRQLRKIKTNYFIVSLAFADLLVSVLVMPFG : 77
d5HT4B : MDKLDANVSSEEGFGSVEKVVLLTFLSTVILMAILGNLLVMVAVCWDRQLRKIKTNYFIVSLAFADLLVSVLVMPFG : 77

h5HT4B : AIELVQDIWIYGEVFCLVRTSLDVLLTTASIFHLCCISLDRYYAICCQPLVYRNKMTPLRIALMLGGCWIIPTFISF : 154
d5HT4B : AIELVQDIWIYGEVFCLVRTSLDVLLTTASIFHLCCISLDRYYAICCQPLVYRNKMTPLRIALMLGGCWIIPMFISF : 154

h5HT4B : LPIMQGWNNIGIIDLERSLNQGLGQDFHAIEKRKFNQNSNSTYCVFMVNKPYAITCSVVAFYIPFLLMVLAYYRIYV : 231
d5HT4B : LPIMQGWNNIGIIDLERISKPRLGQDLHVIEKRKFNQNSNSTYCIFMVNKPYAITCSVVAFYIPRLLMVLAYYRIYV : 231

h5HT4B : TAKEHAHQIQMLQRAGASSESRPQSADQHSTHRMRTETKAAKTLCIIMGCFCLCWAPFFVTNIVDPFIDYTVPGQVW : 308
d5HT4B : TAKEHAHQIQMLQRAGAPSEGRPQPADQHSTHRMRTETKAAKTLCIIMGCFCLCWAPFFVTNIVDPFIDYTVPGQVW : 308

h5HT4B : TAFLWLGYINSGLNPFLYAFLNKSFRRAFLIILCCDDERYRRPSILGQTVPCSTTTINGSTHVLRDAVECGGQWESQ : 385
d5HT4B : TAFLWLGYINSGLNPFLYAFLNKSFRRAFLIILCCDDERYRRPSILGQTVPCSTTTINGSTHVLRDAVECGGQWESQ : 385

h5HT4B : CHPPATSPLVAAQPSDT : 402
d5HT4B : CHPPATSPLVAAQPSDT : 402
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FIG. 1B

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160                 165                 170                 175

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Gly Leu Gly Gln Asp Phe His Ala Ile Glu Lys Arg Lys Phe Asn Gln
                180                 185                 190

aac tct aac tct acg tac tgt gtc ttc atg gtc aac aag ccc tac gcc   624
Asn Ser Asn Ser Thr Tyr Cys Val Phe Met Val Asn Lys Pro Tyr Ala
            195                 200                 205

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        210                 215                 220

ctg gcc tat tac cgc atc tat gtc aca gct aag gag cat gcc cat cag   720
Leu Ala Tyr Tyr Arg Ile Tyr Val Thr Ala Lys Glu His Ala His Gln
    225                 230                 235

atc cag atg tta caa cgg gca gga gcc tcc tcc gag agc agg cct cag   768
Ile Gln Met Leu Gln Arg Ala Gly Ala Ser Ser Glu Ser Arg Pro Gln
240                 245                 250                 255

tcg gca gac cag cat agc act cat cgc atg agg aca gag acc aaa gca   816
Ser Ala Asp Gln His Ser Thr His Arg Met Arg Thr Glu Thr Lys Ala
                260                 265                 270

gcc aag acc ctg tgc atc atc atg ggt tgc ttc tgc ctc tgc tgg gca   864
Ala Lys Thr Leu Cys Ile Ile Met Gly Cys Phe Cys Leu Cys Trp Ala
            275                 280                 285

cca ttc ttt gtc acc aat att gtg gat cct ttc ata gac tac act gtc   912
Pro Phe Phe Val Thr Asn Ile Val Asp Pro Phe Ile Asp Tyr Thr Val
        290                 295                 300

cct ggg cag gtg tgg act gct ttc ctc tgg ctc ggc tat atc aat tcc   960
Pro Gly Gln Val Trp Thr Ala Phe Leu Trp Leu Gly Tyr Ile Asn Ser
    305                 310                 315

ggg ttg aac cct ttt ctc tac gcc ttc ttg aat aag tct ttt aga cgt
1008
Gly Leu Asn Pro Phe Leu Tyr Ala Phe Leu Asn Lys Ser Phe Arg Arg
320                 325                 330                 335

gcc ttc ctc atc atc ctc tgc tgt gat gat gag cgc tac cga aga cct
1056
Ala Phe Leu Ile Ile Leu Cys Cys Asp Asp Glu Arg Tyr Arg Arg Pro
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tcc att ctg ggc cag act gtc cct tgt tca acc aca acc att aat gga
1104
Ser Ile Leu Gly Gln Thr Val Pro Cys Ser Thr Thr Thr Ile Asn Gly
            355                 360                 365

tcc aca cat gta cta agg gat gca gtg gag tgt ggt ggc cag tgg gag
1152
Ser Thr His Val Leu Arg Asp Ala Val Glu Cys Gly Gly Gln Trp Glu
        370                 375                 380

agt cag tgt cac ccg cca gca act tct cct ttg gtg gct gct cag ccc
1200
Ser Gln Cys His Pro Pro Ala Thr Ser Pro Leu Val Ala Ala Gln Pro
    385                 390                 395
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			20					25					30		
Ala	Ile	Leu	Gly	Asn	Leu	Leu	Val	Met	Val	Ala	Val	Cys	Trp	Asp	Arg
		35					40					45			
Gln	Leu	Arg	Lys	Ile	Lys	Thr	Asn	Tyr	Phe	Ile	Val	Ser	Leu	Ala	Phe
	50					55					60				
Ala	Asp	Leu	Leu	Val	Ser	Val	Leu	Val	Met	Pro	Phe	Gly	Ala	Ile	Glu
65					70					75					80
Leu	Val	Gln	Asp	Ile	Trp	Ile	Tyr	Gly	Glu	Val	Phe	Cys	Leu	Val	Arg
				85					90					95	
Thr	Ser	Leu	Asp	Val	Leu	Leu	Thr	Thr	Ala	Ser	Ile	Phe	His	Leu	Cys
			100					105					110		
Cys	Ile	Ser	Leu	Asp	Arg	Tyr	Tyr	Ala	Ile	Cys	Cys	Gln	Pro	Leu	Val
		115					120					125			
Tyr	Arg	Asn	Lys	Met	Thr	Pro	Leu	Arg	Ile	Ala	Leu	Met	Leu	Gly	Gly
	130					135					140				
Cys	Trp	Val	Ile	Pro	Thr	Phe	Ile	Ser	Phe	Leu	Pro	Ile	Met	Gln	Gly
145					150					155					160
Trp	Asn	Asn	Ile	Gly	Ile	Ile	Asp	Leu	Glu	Arg	Ser	Leu	Asn	Gln	Gly
				165					170					175	
Leu	Gly	Gln	Asp	Phe	His	Ala	Ile	Glu	Lys	Arg	Lys	Phe	Asn	Gln	Asn
			180					185					190		
Ser	Asn	Ser	Thr	Tyr	Cys	Val	Phe	Met	Val	Asn	Lys	Pro	Tyr	Ala	Ile
		195					200					205			
Thr	Cys	Ser	Val	Val	Ala	Phe	Tyr	Ile	Pro	Phe	Leu	Leu	Met	Val	Leu
	210					215					220				
Ala	Tyr	Tyr	Arg	Ile	Tyr	Val	Thr	Ala	Lys	Glu	His	Ala	His	Gln	Ile
225					230					235					240
Gln	Met	Leu	Gln	Arg	Ala	Gly	Ala	Ser	Ser	Glu	Ser	Arg	Pro	Gln	Ser
				245					250					255	
Ala	Asp	Gln	His	Ser	Thr	His	Arg	Met	Arg	Thr	Glu	Thr	Lys	Ala	Ala
			260					265					270		

Lys Thr Leu Cys Ile Ile Met Gly Cys Phe Cys Leu Cys Trp Ala Pro
275 280 285

Phe Phe Val Thr Asn Ile Val Asp Pro Phe Ile Asp Tyr Thr Val Pro
290 295 300

Gly Gln Val Trp Thr Ala Phe Leu Trp Leu Gly Tyr Ile Asn Ser Gly
305 310 315 320

Leu Asn Pro Phe Leu Tyr Ala Phe Leu Asn Lys Ser Phe Arg Arg Ala
325 330 335

Phe Leu Ile Ile Leu Cys Cys Asp Asp Glu Arg Tyr Arg Arg Pro Ser
340 345 350

Ile Leu Gly Gln Thr Val Pro Cys Ser Thr Thr Thr Ile Asn Gly Ser
355 360 365

Thr His Val Leu Arg Asp Ala Val Glu Cys Gly Gly Gln Trp Glu Ser
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Asp Thr

10/018257

SEQUENCE LISTING

<110> Janssen Pharmaceutica NV

<120> Cloning and expression of a novel 5-HT4 receptor

<130> Novel 5HT4B splice variant

<140> PCT/EP00/05592
<141> 2000-06-14

<150> GB/9913850.5
<151> 1999-06-14

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<170> PatentIn Ver. 2.1

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tca gtg gag aag gtg gtg ctg ctc acg ttt ctc tcg acg gtt atc ctg   96
Ser Val Glu Lys Val Val Leu Leu Thr Phe Leu Ser Thr Val Ile Leu
                  20                  25                  30

atg gcc atc ttg ggg aac ctg ctg gtg atg gtg gct gtg tgc tgg gac  144
Met Ala Ile Leu Gly Asn Leu Leu Val Met Val Ala Val Cys Trp Asp
              35                  40                  45

agg cag ctc agg aaa ata aaa aca aat tat ttc att gta tct ctt gct  192
Arg Gln Leu Arg Lys Ile Lys Thr Asn Tyr Phe Ile Val Ser Leu Ala
          50                  55                  60

ttt gcg gat ctg ctg gtt tcg gtg ctg gtg atg ccc ttt ggt gcc att  240
Phe Ala Asp Leu Leu Val Ser Val Leu Val Met Pro Phe Gly Ala Ile
      65                  70                  75

gag ctg gtt caa gac atc tgg att tat ggg gag gtg ttt tgt ctt gtt  288
Glu Leu Val Gln Asp Ile Trp Ile Tyr Gly Glu Val Phe Cys Leu Val
  80                  85                  90                  95

cgg aca tct ctg gac gtc ctg ctc aca acg gca tcg att ttt cac ctg  336
Arg Thr Ser Leu Asp Val Leu Leu Thr Thr Ala Ser Ile Phe His Leu
                 100                 105                 110

tgc tgc att tct ctg gat agg tat tac gcc atc tgc tgc cag cct ttg  384
Cys Cys Ile Ser Leu Asp Arg Tyr Tyr Ala Ile Cys Cys Gln Pro Leu
             115                 120                 125

gtc tat agg aac aag atg acc cct ctg cgc atc gca tta atg ctg gga  432
Val Tyr Arg Asn Lys Met Thr Pro Leu Arg Ile Ala Leu Met Leu Gly
         130                 135                 140

ggc tgc tgg gtc atc ccc acg ttt att tct ttt ctc cct ata atg caa  480
Gly Cys Trp Val Ile Pro Thr Phe Ile Ser Phe Leu Pro Ile Met Gln
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AMENDED SHEET